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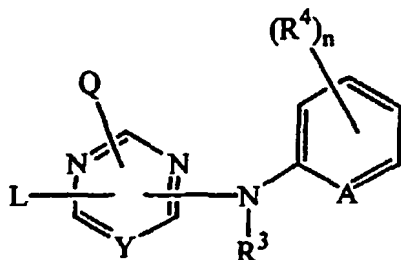
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(54) Title: RATE-CONTROLLED PARTICLES



(I)

(57) Abstract: Rate-controlled
particles, comprising compounds of
formula (I) as a solid dispersion.

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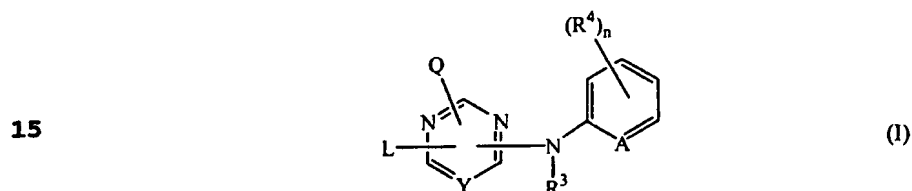
Rate-controlled particles

Specification

5

The present invention concerns pharmaceutical compositions in the form of rate-controlled particles, comprising compounds of the formula (I) to (VI)

10 (I) is an antiviral compound of formula



a N-oxide, a pharmaceutically acceptable addition salt or a
20 stereochemically isomeric form thereof, wherein

Y is CR⁵ or N;

A is CH, CR⁴ or N;

n is 0, 1, 2, 3 or 4;

25 Q is -NR¹R² or when Y is CR⁵ then Q may also be hydrogen;

R¹ and R² are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxycarbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)-amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of
30 the aforementioned C₁₋₁₂alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxy-C₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or
35 di(C₁₋₆alkyl)amino, aryl and Het; or

R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄-alkylidene;

R³ is hydrogen, aryl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxy-carbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxycarbonyl; and
40 each R⁴ independently is hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, or when Y is CR⁵ then R⁴ may also represent C₁₋₆alkyl substituted with cyano or aminocarbonyl;

45 R⁵ is hydrogen or C₁₋₄alkyl;

L is -X¹-R⁶ or -X²-Alk-R⁷ wherein

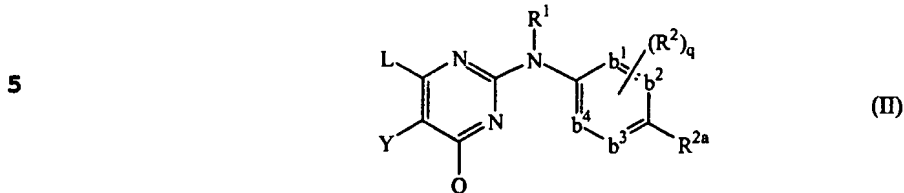
- 5 R^6 and R^7 each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylcarbonyl, C_{1-6} alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl; or when Y is CR^5 then R^6 and R^7 may also be selected from phenyl substituted with one, two, three, four or five substituents each independently selected from aminocarbonyl, trihalomethyloxy and trihalomethyl; or when Y is N then
- 10 R^6 and R^7 may also be selected from indanyl or indolyl, each of said indanyl or indolyl may be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylcarbonyl, C_{1-6} alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl;
- 15 X^1 and X^2 are each independently $-NR^3-$, $-NH-NH-$, $-N=N-$, $-O-$, $-S-$, $-S(=O)-$ or $-S(=O)_2-$;
- Alk is C_{1-4} alkanediyl; or
- when Y is CR^5 then L may also be selected from C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{3-7} cycloalkyl, or C_{1-10} alkyl
- 20 substituted with one or two substituents independently selected from C_{3-7} cycloalkyl, indanyl, indolyl and phenyl, wherein said phenyl, indanyl and indolyl may be substituted with one, two, three, four or where possible five substituents each independently selected from halo, hydroxy,
- 25 C_{1-6} alkyl, C_{1-6} alkyloxy, cyano, aminocarbonyl, C_{1-6} alkyloxycarbonyl, formyl, nitro, amino, trihalomethyl, trihalomethyloxy and C_{1-6} alkylcarbonyl;
- aryl is phenyl or phenyl substituted with one, two, three, four
- 30 or five substituents each independently selected from halo, C_{1-6} alkyl, C_{1-6} alkyloxy, cyano, nitro and trifluoromethyl;
- Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl,
- 35 tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said
- 40 aromatic heterocyclic radical may optionally be substituted with hydroxy.

The compounds of formula (I) can be prepared according to the methods described in the patent applications with application

45 number PCT/EP99/02043 and PCT/EP99/02044.

3

(II) is an antiviral compound of formula



10 the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

-b¹=b²-C(R^{2a})=b³-b⁴= represents a bivalent radical of formula

-CH=CH-C(R^{2a})=CH-CH= (b-1);

15 -N=CH-C(R^{2a})=CH-CH= (b-2);

-CH=N-C(R^{2a})=CH-CH= (b-3);

-N=CH-C(R^{2a})=N-CH= (b-4);

-N=CH-C(R^{2a})=CH-N= (b-5);

-CH=N-C(R^{2a})=N-CH= (b-6);

20 -N=N-C(R^{2a})=CH-CH= (b-7);

q is 0, 1, 2; or where possible q is 3 or 4;

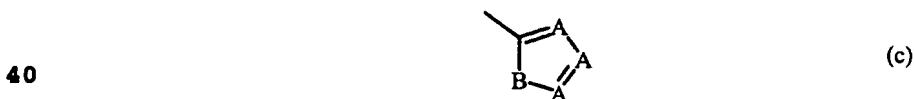
R¹ is hydrogen, aryl, formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl;

25 R^{2a} is cyano, aminocarbonyl, mono- or di(methyl)aminocarbonyl, C₁₋₆alkyl substituted with cyano, aminocarbonyl or mono- or di(methyl)aminocarbonyl, C₂₋₆alkenyl substituted with cyano, or C₂₋₆alkynyl substituted with cyano;

each R² independently is hydroxy, halo, C₁₋₆alkyl optionally sub-

30 stituted with cyano or -C(=O)R⁶, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more halogen atoms or cyano, C₂₋₆alkynyl optionally substituted with one or more halogen atoms or cyano, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino,

35 polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶ or a radical of formula



wherein each A independently is N, CH or CR⁶;

B is NH, O, S or NR⁶;

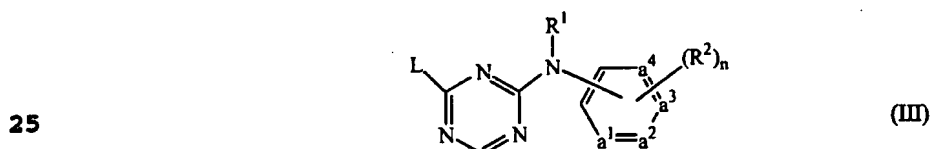
45 p is 1 or 2; and

R⁶ is methyl, amino, mono- or dimethylamino or polyhalomethyl;

- L is C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₇cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from
- * C₃₋₇cycloalkyl,
 - 5 * indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C₁₋₆alkylcarbonyl,
 - 10 * phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; or
- 15 L is -X-R³ wherein
 R³ is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; and
- 20 X is -NR¹-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)- or -S(=O)₂-;
- Q represents hydrogen, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl or -NR⁴R⁵; and
- 25 R⁴ and R⁵ are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxy-carbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of the aforementioned C₁₋₁₂alkyl groups may optionally and each individually be
- 30 substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxy-carbonyl, cyano, amino, imino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶, aryl and Het; or
- 35 R⁴ and R⁵ taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄alkylidene;
- Y represents hydroxy, halo, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more halogen atoms, C₂₋₆alkynyl
- 40 optionally substituted with one or more halogen atoms, C₁₋₆alkyl substituted with cyano or -C(=O)R⁶, C₁₋₆alkyloxy, C₁₋₆alkyloxy-carbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶ or aryl;
- 45

- aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, cyano, nitro, polyhaloC₁₋₆alkyl and polyhaloC₁₋₆alkyloxy;
- 5 Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted
- 10 with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy.
- 15 The compounds of formula (II) can be prepared according to the methods described in the US patent applications with application number 60/143962 and 60/107792.

20 (III) is an antiviral compound of formula

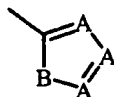


- a N-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof, wherein
- 30 -a¹=a²-a³=a⁴- represents a bivalent radical of formula
- | | |
|---------------|--------|
| -CH=CH-CH=CH- | (a-1); |
| -N=CH-CH=CH- | (a-2); |
| -N=CH-N=CH- | (a-3); |
| -N=CH-CH=N- | (a-4); |
| -N=N-CH=CH- | (a-5); |

- 35 n is 0, 1, 2, 3 or 4; and in case -a¹=a²-a³=a⁴- is (a-1), then n may also be 5;
- R¹ is hydrogen, aryl, formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl; and
- 40 each R² independently is hydroxy, halo, C₁₋₆alkyl optionally substituted with cyano or -C(=O)R⁴, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more halogen atoms or cyano, C₂₋₆alkynyl optionally substituted with one or more
- 45 halogen atoms or cyano, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino,

polyhalomethyl, polyhalomethyloxy, polyhalomethylthio,
 $-S(=O)_pR^4$, $-NH-S(=O)_pR^4$, $-C(=O)R^4$, $-NHC(=O)H$, $-C(=O)NHNH_2$,
 $-NHC(=O)R^4$, $-C(=NH)R^4$ or a radical of formula

5



(c)

wherein each A independently is N, CH or CR^4 ;

B is NH, O, S or NR^4 ;

10 p is 1 or 2; and

R^4 is methyl, amino, mono- or dimethylamino or polyhalo-
 methyl;

L is C_4-10 alkyl, C_2-10 alkenyl, C_2-10 alkynyl, C_3-7 cycloalkyl,
 whereby each of said aliphatic group may be substituted with

15 one or two substituents independently selected from

* C_3-7 cycloalkyl,

* indolyl or isoindolyl, each optionally substituted with
 one, two, three or four substituents each independently
 selected from halo, C_1-6 alkyl, hydroxy, C_1-6 alkyloxy,
 20 cyano, aminocarbonyl, nitro, amino, polyhalomethyl, poly-
 halomethyloxy and C_1-6 alkylcarbonyl,

* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl,
 wherein each of said aromatic rings may optionally be
 substituted with one, two, three, four or five substi-
 25 tuents each independently selected from the substituents
 defined in R^2 ; or

L is $-X-R^3$ wherein

R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazi-
 nyl, wherein each of said aromatic rings may optionally
 30 be substituted with two, three, four or five substituents
 each independently selected from the substituents defined
 in R^2 ; and

X is $-NR^1-$, $-NH-NH-$, $-N=N-$, $-O-$, $-C(=O)-$, $-CHOH-$, $-S-$,
 $-S(=O)-$ or $-S(=O)_2-$;

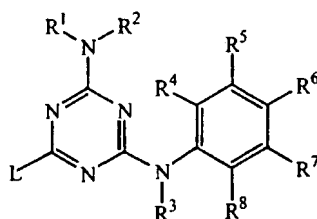
35 aryl is phenyl or phenyl substituted with one, two, three, four
 or five substituents each independently selected from halo,
 C_1-6 alkyl, C_3-7 cycloalkyl, C_1-6 alkyloxy, cyano, nitro, poly-
 halo C_1-6 alkyl and polyhalo C_1-6 alkyloxy.

40 The compounds of formula (III) can be prepared according to the
 methods described in the US patent application with application
 number 60/107799.

45

(IV) is an antiviral compound of formula

5



(IV)

10

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

R¹ and R² are each independently selected from hydrogen; hydroxy;

15 amino; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyl-oxycarbonyl; Ar¹; mono- or di(C₁₋₆alkyl)amino; mono- or di(C₁₋₆alkyl)aminocarbonyl; dihydro-2(3H)-furanone; C₁₋₆alkyl substituted with one or two substituents each independently

20 selected from amino, imino, aminocarbonyl, aminocarbonyl-amino, hydroxy, hydroxyc₁₋₆alkyloxy, carboxyl, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkyloxycarbonyl and thienyl; or

R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₆alkyl)aminoC₁₋₄-alkylidene;

25 R³ is hydrogen, Ar¹, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxy-carbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxycarbonyl; and R⁴, R⁵, R⁶, R⁷ and R⁸ are each independently selected from hydro-

gen, hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, amino-carbonyl, nitro, amino, trihalomethyl or trihalomethyloxy ;

30 L is C₁₋₁₀alkyl; C₃₋₁₀alkenyl; C₃₋₁₀alkynyl; C₃₋₇cycloalkyl; or is C₁₋₁₀alkyl substituted with one or two substituents independently selected from C₃₋₇cycloalkyl; indolyl or indolyl substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalo-methyloxy, C₁₋₆alkylcarbonyl; phenyl or phenyl substituted with one, two, three, four or five substituents each indepen-

35 dently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalo-methyloxy, C₁₋₆alkylcarbonyl; and,

40 Ar¹ is phenyl, or phenyl substituted with one, two or three substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro or trifluoromethyl; with the proviso that compounds (a) to (o)

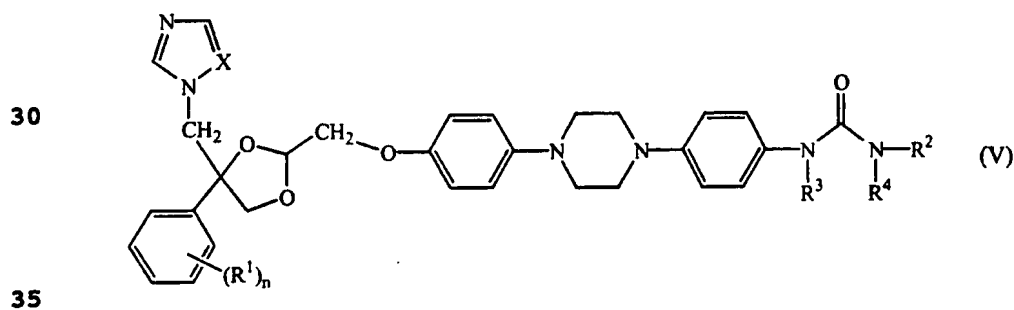
45

Co. No.	Alk	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
5	a	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	CH ₃	H	H	H
	b	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	NO ₂	H	H
	c	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	C ₆ H ₅	H	H	H	H
	d	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	NO ₂	H	CH ₃	H
	e	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	NH ₂	H	H
10	f	4-(2-methylpropyl)phenylmethyl	H/H	H	H	CF ₃	H	H
	g	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	Cl	H
	h	4-(2-methylpropyl)phenylmethyl	H/H	H	H	H	H	H
	i	3,4-dimethoxyphenylmethyl	H/H	H	H	H	H	H
	j	2,3-dimethoxyphenylmethyl	H/H	H	H	H	H	H
15	k	3,4-diethoxyphenylmethyl	H/H	H	H	H	H	H
	l	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	H	H	H
	m	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	t-Bu	OH	t-Bu
	n	Phenylmethyl	H/H	H	CH ₃	H	H	H
	o	Phenylmethyl	H/H	H	H	H	H	H

20 are not included.

The compounds of formula (IV) can be prepared according to the methods described in EP-A-0834507.

25 (V) is an antifungal compound of formula



the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein *n* is zero, 1, 2 or 3;

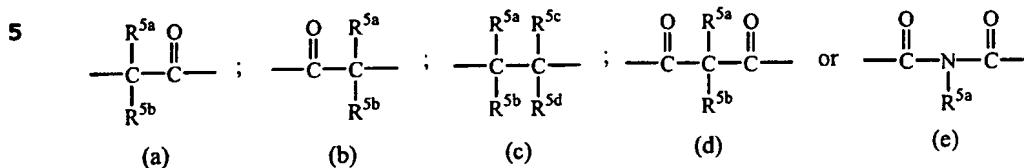
40 X is N or CH;

each R¹ independently is halo, nitro, cyano, amino, hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy or trifluoromethyl;

R² is hydrogen; C₃₋₇alkenyl; C₃₋₇alkynyl, aryl; C₃₋₇cycloalkyl; C₁₋₆alkyl or C₁₋₆alkyl substituted with hydroxy, C₁₋₄alkyloxy, C₃₋₇cycloalkyl or aryl;

45 R³ and R⁴ each independently are hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl or aryl; or

R³ and R⁴ taken together form a bivalent radical -R³-R⁴- of formula:



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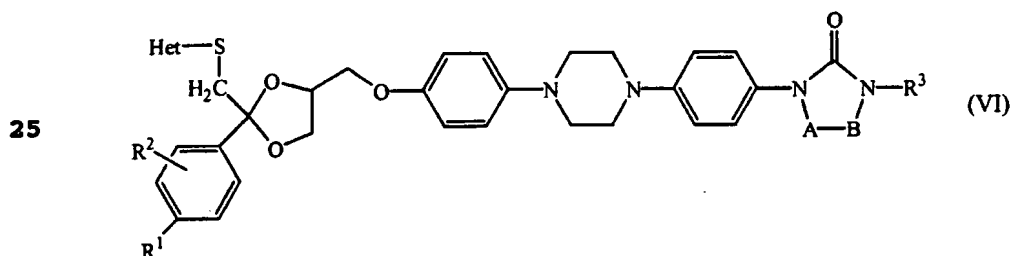
wherein R^{5a}, R^{5b}, R^{5c}, R^{5d} each independently are hydrogen, C₁₋₆alkyl or aryl; and

aryl is phenyl or phenyl substituted with one, two or three substituents selected from halo, nitro, cyano, amino, hydroxy,

15 C₁₋₄alkyl, C₁₋₄alkyloxy or trifluoromethyl.

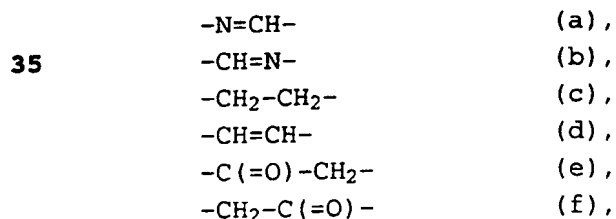
The compounds of formula (V) can be prepared according to the methods described in WO 99/02523.

20 (VI) is an apolipoprotein-B synthesis inhibitor of formula



30

the N-oxides, the stereochemically isomeric forms thereof, and the pharmaceutically acceptable acid addition salts, wherein A and B taken together form a bivalent radical of formula :



40 in the bivalent radicals of formula (a) and (b) the hydrogen atom may be replaced by C₁₋₆alkyl; in the bivalent radicals of formula (c), (d), (e), (f), one or two hydrogen atoms may be replaced by C₁₋₆alkyl;

R¹ is hydrogen, C₁₋₆alkyl or halo;

45 R² is hydrogen or halo;

R³ is hydrogen; C₁₋₈alkyl; C₃₋₆cycloalkyl; or C₁₋₈alkyl substituted with hydroxy, oxo, C₃₋₆cycloalkyl or aryl;

- Het is a heterocycle selected from the group consisting of pyridine; pyridine substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino or aryl; pyrimidine;
- 5 pyrimidine substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino or aryl; tetrazole; tetrazole substituted with C₁₋₆alkyl or aryl; triazole; triazole substituted with one or two substituents selected from C₁₋₆alkyl,
- 10 hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino; thiadiazole; thiadiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino; oxadiazole substituted with one or two substituents
- 15 selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; imidazole; imidazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; thiazole; thiazole substituted with one or
- 20 two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; oxazole; oxazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino;
- 25 aryl is phenyl or phenyl substituted with C₁₋₆alkyl or halo.

The heterocyclic radical "Het" is bound to the sulfur atom via a carbon atom.

- 30 The compounds of formula (VI) can be prepared according to the methods described in WO 96/13499.

The particles comprise the compounds of formula (I) to (VI) as a solid dispersion in a polymeric matrix, wherein the poly-

35 meric matrix is consisting of a homo- or copolymer of N-vinylpyrrolidone. Furthermore, the invention concerns a process for manufacturing of such particles and pharmaceutical dosage forms comprising such particles.

- 40 The compounds of formula (I) to (VI) contained in the particles show poor bio-availability.

In order to improve the dissolution characteristics the compounds are dispersed in a polymeric matrix, preferably by using a melt-

45 extrusion process.

11

EP-A 0 240 904 discloses a method for producing solid pharmaceutical forms by extrusion of polymer melts which contain active substances, using as polymers homo- or copolymers of N-vinylpyrrolidone.

5

EP-B 0 580 860 discloses a method for producing solid dispersions of drug substances in a polymeric matrix using a twin screw extruder.

- 10 It is an object of the present invention to provide rate-controlled pharmaceutical forms containing the aforementioned compounds.

We have found that this object is achieved by the particles
15 defined at the outset.

Preferred compounds according to the invention are:

- 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;
20 4-[[2-[(cyanophenyl)amino]-4-pyrimidinyl]amino]-3,5-dimethylbenzonitrile;
4-[[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile;
4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-
25 amino]benzonitrile;
4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]-amino]benzonitrile;
4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;
30 4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile;
4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;
4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-
35 pyrimidinyl]amino]benzonitrile;
4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]amino]benzonitrile;
4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]-amino]benzonitrile;
40 4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-yl]amino]benzonitrile;
1-[4-[4-[4-[(4-(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-yl)methyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-2-imidazolidinone;
45

(-)-[2S-[2alpha,4alpha(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methyl-propyl)-3H-1,2,4-triazol-3-one,

- 5 a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof.

According to the present invention the term "rate-controlled" means that depending on the composition of the matrix the

10 particles can show instant release of the active ingredient or modified release (sustained release).

The compounds according to the invention are homogeneously dispersed in a polymer matrix consisting of a homopolymer of

15 N-vinylpyrrolidone or, preferably, a copolymer of N-vinylpyrrolidone. A preferred copolymer is a copolymer of N-vinylpyrrolidone and vinyl acetate, especially a copolymer obtained from 60% b.w. of NVP and 40% b.w. of vinylacetate.

- 20 The polymers show Fikentscher K values of from 17 to 90, preferably a K value of 30 (for the definition of the K value see "H. Fikentscher, Cellulose-Chemie" (1932), 58-64 and 71-74).

The polymeric matrix component is used in amounts of from 40 to

25 70, preferably of from 50 to 65% b.w. of the total weight of the particles.

In a preferred embodiment of the invention the polymeric matrix further comprises a surfactant, preferably a surfactant with

30 a HLB-value of 10-18 (HLB: Hydrophilic Lipophilic Balance). Especially preferred surfactants are selected from the group consisting of low molecular weight polyoxyethylene polyoxypropylene block copolymers with a mean molecular weight of 1000 to 6000 g/mol, and hydrogenated castor oil which can be

35 modified with polyethylene glycol.

The amounts of surfactants used lies in the range of up to 20% b.w., preferably 5 to 15% b.w., of the particles.

- 40 In another preferred embodiment the matrix further comprises an organic carboxylic acid in amounts of up to 5% b.w. of the particles.

In another preferred embodiment of the invention the polymeric matrix further comprises hydroxypropyl methyl cellulose in

45 amounts of up to 25% b.w., preferably from 5 to 10% b.w..

The particles of the present invention are prepared as solid dispersions of the active compounds in a polymeric matrix. The term "solid dispersion" is well known in the art and means a dispersion consisting of solid components. Preferably solid
5 dispersions are in the form of solid solutions wherein the active ingredients are molecularly dispersed in the polymeric matrix.

Such solid dispersion is preferably obtained by forming a homogeneous mixture of the components in the form of a melt,
10 extruding said melt and shaping of the extrudate. The melting is effected by the input of thermal and/or mechanic energy.

Depending on the composition of the matrix, the melting takes place in the range of from 40°C to 190°C, preferably 50 to 150°C.
15 The suitable temperature range depends on the glass transition temperature of the polymer component, the properties of the active ingredients and further additives. The optimal temperature range can be established by a few simple tests.

20 The mixing of the active substances with the polymer and additional components of the matrix can take place before or after the melting of the polymer. Preferably the process is solvent-free which means that no additional organic solvents or water are added.

25 The plastification and melting preferably can take place in an extruder, a kneader or a mixing reactor, preferably in an extruder having one or more screws which may rotate in the same direction or opposite directions, especially in a twin screw
30 extruder. The latter can be operated with or without kneading elements, but use of kneading elements is preferred because mixing is better.

The still plastic material is extruded through a die or a breaker
35 plate and then shaped into particles. This may be effected by milling and subsequent sieving the cooled extrudate. The preferred particle size for instant release forms lies in the range of from 0.5 to 1.5 mm.

40 The particles, optionally together with conventional pharmaceutically acceptable excipients, may be further processed to conventional pharmaceutical dosage forms such as tablets, pastilles, suppositories, or be packed in capsules.

45 It is possible and particularly advantageous to produce pharmaceutical forms with rate-controlled release and improved dissolution rates of the active ingredients. This was not to be

expected in view of the low solubility of the active ingredients in aqueous media.

Examples

5

General method

Powder mixes of the components were melt kneaded at 145°C for 5 min.. After cooling the solidified melts were ground and
 10 sieved. The sieve fraction 0.5-1.5 mm was used for the dissolution tests.

The composition of the individual powder mixes is listed in Table 1.

15

Table 1

Example No.	1	2	3	4	5	6
Active ingredient ¹⁾	30	30	30	30	30	40
20 VP-VAC-copolymer ²⁾	65	55	55	60	55	47,1
Surfactant ³⁾	5	15		5	5	4,3
Citric acid				5		
HPMC					10	8,6
Surfactant ⁴⁾			15			

- 25 1) 4-[[4-[2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]-benzonitrile
 2) Kollidon® VA64, VP/VAC = 60/40, BASF Aktiengesellschaft
 3) PEG-n-hydrogenated Castoroil
 4) polyoxyethylene polyoxypropylene blockcopolymer, mean mol.
 30 weight 4000 g/mol

The dissolution tests were carried out according to USP XXIII, paddle model, pH no change test, 0.1 M HCl, at 37°C, 100 rpm

35

40

45

The results are listed in Table 2.

Table 2: Dissolution Rates of particles according to examples 1-6

5

time [min]	Dissolution [%]				time [min]	Dissolution [%]	
	Ex. 1 (IR)	Ex. 2 (IR)	Ex. 3 (IR)	Ex. 4 (IR)		Ex. 5 (SR)	Ex. 6 (SR)
5	53	65	58	57	1		
10	73	86	88	82	2		
15	77	91	95	89	3		
20	81	91	96	93	4		
30	87	94	99	94	6		
60	92	93	96	94	8	96	95
120	93	94	97	95			
	IR: Instant Release					SR: Sustained Release	

20 DSC-Measurements were performed with the formulations according to examples 1 to 6 in open pans (air) at temperatures of from 20 → 250°C, with a heating rate of 10°C per minute. There is no indication of crystalline drug substance in the solid dispersions.

25

30

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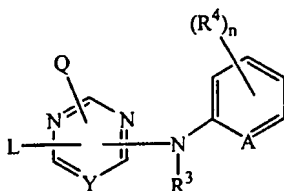
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Claims

1. Rate-controlled release particles, comprising a compound of
 5 formula I

10



(I)

15

a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein

15

Y is CR⁵ or N;

A is CH, CR⁴ or N;

n is 0, 1, 2, 3 or 4;

Q is -NR¹R² or when Y is CR⁵ then Q may also be hydrogen;

20

R¹ and R² are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxycarbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)-amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of the aforementioned C₁₋₁₂alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxy-C₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or di(C₁₋₆alkyl)amino, aryl and Het; or

25

30

R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄-alkylidene;

35

R³ is hydrogen, aryl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxy-carbonyl; and

each R⁴ independently is hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, or when Y is CR⁵ then R⁴ may also represent C₁₋₆alkyl substituted with cyano or amino-carbonyl;

40

R⁵ is hydrogen or C₁₋₄alkyl;

L is -X¹-R⁶ or -X²-Alk-R⁷ wherein

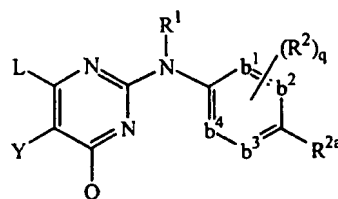
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R⁶ and R⁷ each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy,

5 C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkyl-
oxycarbonyl, formyl, cyano, nitro, amino, and tri-
fluoromethyl; or when Y is CR⁵ then R⁶ and R⁷ may
also be selected from phenyl substituted with one,
two, three, four or five substituents each indepen-
dently selected from aminocarbonyl, trihalomethyloxy
and trihalomethyl; or when Y is N then R⁶ and R⁷ may
also be selected from indanyl or indolyl, each of
said indanyl or indolyl may be substituted with one,
two, three, four or five substituents each
independently selected from halo, hydroxy, C₁₋₆alkyl,
C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl,
formyl, cyano, nitro, amino, and trifluoromethyl;
10 X¹ and X² are each independently -NR³-, -NH-NH-, -N=N-,
-O-, -S-, -S(=O)- or -S(=O)₂-;
15 Alk is C₁₋₄alkanediyl; or
when Y is CR⁵ then L may also be selected from C₁₋₁₀alkyl,
C₃₋₁₀alkenyl, C₃₋₁₀alkynyl, C₃₋₇cycloalkyl, or C₁₋₁₀alkyl
substituted with one or two substituents independently
selected from C₃₋₇cycloalkyl, indanyl, indolyl and
20 phenyl, wherein said phenyl, indanyl and indolyl may be
substituted with one, two, three, four or where possible
five substituents each independently selected from halo,
hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl,
C₁₋₆alkyloxycarbonyl, formyl, nitro, amino, trihalomethyl,
25 trihalomethyloxy and C₁₋₆alkylcarbonyl;
aryl is phenyl or phenyl substituted with one, two, three,
four or five substituents each independently selected
from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro and
trifluoromethyl;
30 Het is an aliphatic or aromatic heterocyclic radical;
said aliphatic heterocyclic radical is selected from
pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl,
morpholinyl, tetrahydrofuranyl and tetrahydrothienyl
wherein each of said aliphatic heterocyclic radical may
optionally be substituted with an oxo group; and said
aromatic heterocyclic radical is selected from pyrrolyl,
furanly, thienyl, pyridyl, pyrimidinyl, pyrazinyl and
pyridazinyl wherein each of said aromatic heterocyclic
40 radical may optionally be substituted with hydroxy,

or a compound of formula

5



(II)

10 the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

-b¹=b²-C(R²ᵃ)=b³-b⁴= represents a bivalent radical of formula

15

-CH=CH-C(R²ᵃ)=CH-CH= (b-1);

-N=CH-C(R²ᵃ)=CH-CH= (b-2);

-CH=N-C(R²ᵃ)=CH-CH= (b-3);

-N=CH-C(R²ᵃ)=N-CH= (b-4);

-N=CH-C(R²ᵃ)=CH-N= (b-5);

-CH=N-C(R²ᵃ)=N-CH= (b-6);

20

-N=N-C(R²ᵃ)=CH-CH= (b-7);

q is 0, 1, 2; or where possible *q* is 3 or 4;

*R*¹ is hydrogen, aryl, formyl, C₁-₆alkylcarbonyl, C₁-₆alkyl, C₁-₆alkyloxycarbonyl, C₁-₆alkyl substituted with formyl, C₁-₆alkylcarbonyl, C₁-₆alkyloxycarbonyl;

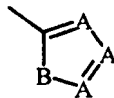
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*R*²ᵃ is cyano, aminocarbonyl, mono- or di(methyl)amino-carbonyl, C₁-₆alkyl substituted with cyano, amino-carbonyl or mono- or di(methyl)aminocarbonyl, C₂-₆alkenyl substituted with cyano, or C₂-₆alkynyl substituted with cyano;

30

each *R*² independently is hydroxy, halo, C₁-₆alkyl optionally substituted with cyano or -C(=O)*R*⁶, C₃-₇cycloalkyl, C₂-₆alkenyl optionally substituted with one or more halogen atoms or cyano, C₂-₆alkynyl optionally substituted with one or more halogen atoms or cyano, C₁-₆alkyloxy, C₁-₆alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁-₆alkyl)amino, polyhalomethyl, polyhalomethoxy, polyhalomethylthio, -S(=O)_{*p*}*R*⁶, -NH-S(=O)_{*p*}*R*⁶, -C(=O)*R*⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)*R*⁶, -C(=NH)*R*⁶ or a radical of formula

40



(c)

45

wherein each A independently is N, CH or CR⁶;

B is NH, O, S or NR⁶;

p is 1 or 2; and

R⁶ is methyl, amino, mono- or dimethylamino or polyhalomethyl;

5

L is C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₇cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

* C₃₋₇cycloalkyl,

10

* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C₁₋₆alkyl-carbonyl,

15

* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; or

20

L is -X-R³ wherein

R³ is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; and

25

X is -NR¹-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)- or -S(=O)₂-;

Q represents hydrogen, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl or -NR⁴R⁵; and

30

R⁴ and R⁵ are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxy carbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of the aforementioned C₁₋₁₂alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxy carbonyl, cyano, amino, imino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶, aryl and Het; or

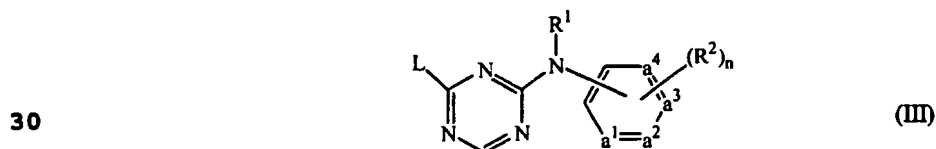
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R⁴ and R⁵ taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄-alkylidene;

45

- Y represents hydroxy, halo, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more halogen atoms, C₂₋₆alkynyl optionally substituted with one or more halogen atoms, C₁₋₆alkyl substituted with cyano or
 5 -C(=O)R⁶, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶ or aryl;
 10 aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, cyano, nitro, polyhaloC₁₋₆alkyl and polyhaloC₁₋₆alkyloxy;
 Het is an aliphatic or aromatic heterocyclic radical;
 15 said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said
 20 aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy,
 25 or a compound of formula



- a N-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof,
 35 wherein

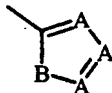
-a¹=a²-a³=a⁴- represents a bivalent radical of formula

- 40
- | | |
|---------------|--------|
| -CH=CH-CH=CH- | (a-1); |
| -N=CH-CH=CH- | (a-2); |
| -N=CH-N=CH- | (a-3); |
| -N=CH-CH=N- | (a-4); |
| -N=N-CH=CH- | (a-5); |

n is 0, 1, 2, 3 or 4; and in case -a¹=a²-a³=a⁴- is (a-1), then n may also be 5;

- 45 R¹ is hydrogen, aryl, formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl; and

each R^2 independently is hydroxy, halo, C_{1-6} alkyl optionally substituted with cyano or $-C(=O)R^4$, C_{3-7} cycloalkyl, C_{2-6} alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6} alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6} alkyloxy, C_{1-6} alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6} alkyl)amino, polyhalomethyl, polyhalomethoxy, polyhalomethylthio, $-S(=O)_pR^4$, $-NH-S(=O)_pR^4$, $-C(=O)R^4$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^4$, $-C(=NH)R^4$ or a radical of formula



(c)

wherein each A independently is N, CH or CR^4 ;
 B is NH, O, S or NR^4 ;
 p is 1 or 2; and
 R^4 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C_{4-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

- * C_{3-7} cycloalkyl,
- * indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6} alkyl, hydroxy, C_{1-6} alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethoxy and C_{1-6} alkyl-carbonyl,
- * phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2 ; or

L is $-X-R^3$ wherein

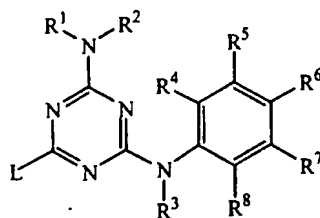
R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with two, three, four or five substituents each independently selected from the substituents defined in R^2 ; and

X is $-NR^1-$, $-NH-NH-$, $-N=N-$, $-O-$, $-C(=O)-$, $-CHOH-$, $-S-$, $-S(=O)-$ or $-S(=O)_2-$;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkyloxy, cyano, nitro, polyhalo C_{1-6} alkyl and polyhalo C_{1-6} alkyloxy,

or a compound of formula

5



(IV)

10

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

R¹ and R² are each independently selected from hydrogen;

15

hydroxy; amino; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxy carbonyl; Ar¹; mono- or di(C₁₋₆alkyl)amino; mono- or di(C₁₋₆alkyl)aminocarbonyl; dihydro-2(3H)-furanone; C₁₋₆alkyl substituted with one or two substituents each independently selected from amino, imino, aminocarbonyl, aminocarbonylamino, hydroxy, hydroxyC₁₋₆alkyloxy, carboxyl, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkyloxy carbonyl and thienyl; or

20

R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₆alkyl)aminoC₁₋₄alkylidene;

25

R³ is hydrogen, Ar¹, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxy carbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxy carbonyl; and

30

R⁴, R⁵, R⁶, R⁷ and R⁸ are each independently selected from hydrogen, hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethyloxy ;

L is C₁₋₁₀alkyl; C₃₋₁₀alkenyl; C₃₋₁₀alkynyl; C₃₋₇cycloalkyl; or

35

L is C₁₋₁₀alkyl substituted with one or two substituents independently selected from C₃₋₇cycloalkyl; indolyl or indolyl substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C₁₋₆alkylcarbonyl; phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C₁₋₆alkylcarbonyl; and,

45

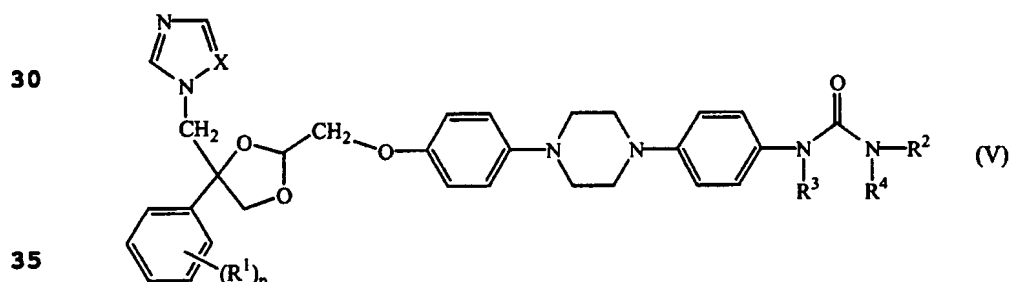
23

Ar¹ is phenyl, or phenyl substituted with one, two or three substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro or trifluoromethyl; with the proviso that compounds (a) to (o)

Co. No.	Alk	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
a	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	CH ₃	H	H	H	H
b	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NO ₂	H	H
c	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	C ₆ H ₅	H	H	H	H	H
d	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	NO ₂	H	CH ₃	H	H
e	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NH ₂	H	H
f	4-(2-methylpropyl)phenylmethyl	H/H	H	H	CF ₃	H	H	H
g	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	Cl	H	H
h	4-(2-methylpropyl)phenylmethyl	H/H	H	H	H	H	H	H
i	3,4-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
j	2,3-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
k	3,4-diethoxyphenylmethyl	H/H	H	H	H	H	H	H
l	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	H	H	H	H
m	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	t-Bu	OH	t-Bu	H
n	Phenylmethyl	H/H	H	CH ₃	H	H	H	H
o	Phenylmethyl	H/H	H	H	H	H	H	H

are not included,

or a compound of formula



the N-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein

n is zero, 1, 2 or 3;

X is N or CH;

each R¹ independently is halo, nitro, cyano, amino, hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy or trifluoromethyl;

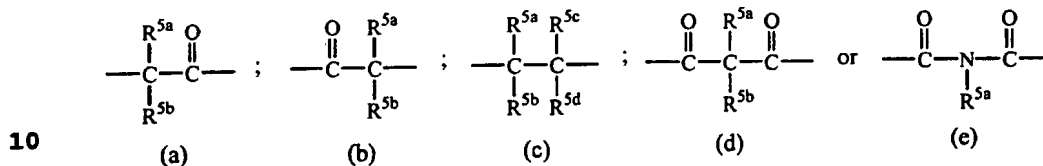
R² is hydrogen; C₃₋₇alkenyl; C₃₋₇alkynyl, aryl; C₃₋₇cycloalkyl; C₁₋₆alkyl or C₁₋₆alkyl substituted with hydroxy, C₁₋₄alkyloxy, C₃₋₇cycloalkyl or aryl;

24

R^3 and R^4 each independently are hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl or aryl; or

R^3 and R^4 taken together form a bivalent radical $-R^3-R^4-$ of formula:

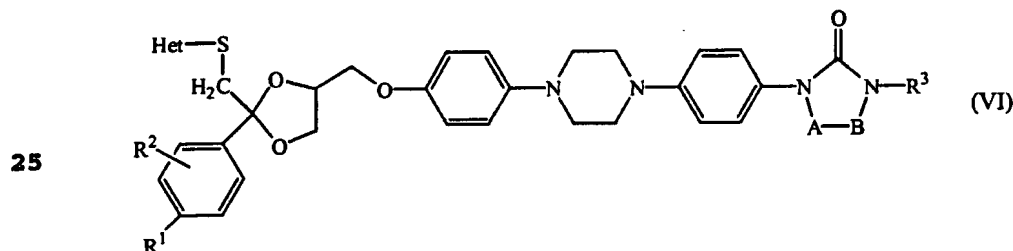
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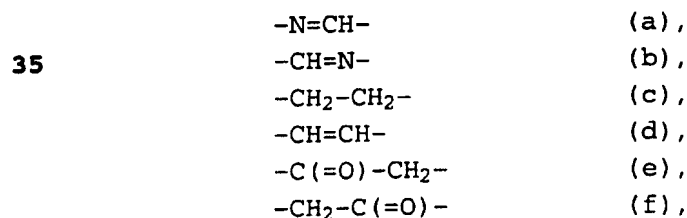
wherein R^{5a} , R^{5b} , R^{5c} , R^{5d} each independently are hydrogen, C_{1-6} alkyl or aryl; and
 15 aryl is phenyl or phenyl substituted with one, two or three substituents selected from halo, nitro, cyano, amino, hydroxy, C_{1-4} alkyl, C_{1-4} alkyloxy or trifluoromethyl,

or a compound of formula

20



30 the *N*-oxides, the stereochemically isomeric forms thereof, and the pharmaceutically acceptable acid addition salts, wherein A and B taken together form a bivalent radical of formula :



40 in the bivalent radicals of formula (a) and (b) the hydrogen atom may be replaced by C_{1-6} alkyl; in the bivalent radicals of formula (c), (d), (e), (f), one or two hydrogen atoms may be replaced by C_{1-6} alkyl;

R^1 is hydrogen, C_{1-6} alkyl or halo;

45 R^2 is hydrogen or halo;

R^3 is hydrogen; C_{1-8} alkyl; C_{3-6} cycloalkyl; or C_{1-8} alkyl substituted with hydroxy, oxo, C_{3-6} cycloalkyl or aryl;

Het is a heterocycle selected from the group consisting of pyridine; pyridine substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino or aryl; 5 pyrimidine; pyrimidine substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino or aryl; tetrazole; tetrazole substituted with C₁₋₆alkyl or aryl; triazole; triazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino; thia- 10 diazole; thiadiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino; oxadiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; imidazole; imidazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; thia- 20 zole; thiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; oxazole; oxazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; 25 aryl is phenyl or phenyl substituted with C₁₋₆alkyl or halo, and the heterocyclic radical "Het" is bound to the sulfur atom via a carbon atom,

30 as a solid dispersion in a polymeric matrix, wherein the polymeric matrix is consisting of a homo- or copolymer of N-vinylpyrrolidone.

35 2. Particles according to claim 1, wherein the copolymer of N-vinylpyrrolidone is a copolymer with vinyl acetate.

3. Particles according to claim 1 or 2, further comprising a surfactant.

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4. Particles according to claim 3, wherein the surfactant is a PEG-n-hydrogenated castor oil.

45 5. Particles according to any of the claims 1 to 3, wherein the surfactant is a low molecular weight polyoxyethylene polyoxypropylene block copolymer.

6. Particles according to any of the claims 1 to 3, further comprising citric acid in amounts of up to 5 % b.w.
7. Particles according to any of the claims 1 to 6, wherein the
5 homo- or copolymer of N-vinylpyrrolidone is used in amounts of from 40 to 70 % b.w. of the total weight of the dosage form.
8. Particles according to claim 7, wherein the homo- or copoly-
10 mer of N-vinylpyrrolidone is used in amounts of from 50 to 65 % b.w..
9. Particles according to any of the claims 1 to 8, wherein the controlled release is an instant release of the drug.
- 15 10. Particles according to any of the claims 1 to 8, wherein the controlled release is a sustained release.
11. Particles according to claim 10, further comprising hydroxy-
propyl methyl cellulose in amounts of from 5 to 10 % b.w..
20
12. Particles according to any of the claims 1 to 11, obtained by forming a homogeneous mixture of the components in the form of a melt, extruding said mixture and shaping of the extru-
date.
25
13. Particles according to any of the claims 1 to 11, comprising a compound selected from the group consisting of
4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]-
benzonitrile;
30 4-[[2-[(cyanophenyl)amino]-4-pyrimidinyl]amino]-3,5-dimethyl-
benzonitrile;
4-[[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-
pyrimidinyl]-amino]benzonitrile;
4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-
35 amino]benzonitrile;
4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]-
amino]benzonitrile;
4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-
pyrimidinyl]amino]benzonitrile;
40 4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-
pyrimidinyl]-
amino]benzonitrile;
4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenyloxy)-2-
pyrimidinyl]amino]benzonitrile;
45 4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenyloxy)-2-
pyrimidinyl]amino]benzonitrile;

- 4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]-amino]benzonitrile;
4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]benzonitrile;
5 4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-yl]amino]benzonitrile;
1-[[4-[[4-[[4-[(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-3-(1-methylethyl)-2-imidazolidinone;
10 (-)-[2S-[2alpha,4alpha(S*)]]-4-[[4-[[4-[[2-(4-chlorophenyl)-2-[[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methyl-propyl)-3H-1,2,4-triazol-3-one,
a N-oxide, a pharmaceutically acceptable addition salt or a
15 stereochemically isomeric form thereof.

14. Pharmaceutical dosage form, comprising particles according to any of the preceding claims.
- 20 15. Pharmaceutical dosage forms according to claim 13, further comprising one or more pharmaceutically acceptable excipients.

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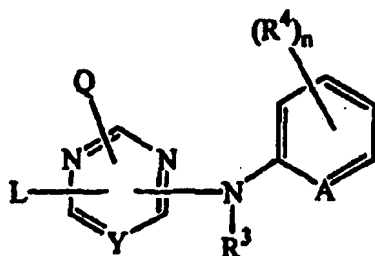
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(54) Title: **RATE-CONTROLLED PARTICLES**



(I)

(57) Abstract: Rate-controlled particles, comprising
compounds of formula (I) as a solid dispersion.

INTERNATIONAL SEARCH REPORT

Internat / Application No

PCT/EP 00/09149

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/48 C07D251/18 C07D239/50 C07D403/12 C07D521/00
C07D405/14 A61K31/505 A61P35/00 A61K9/16 A61K9/14

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 872 233 A (JANSSEN) 21 October 1998 (1998-10-21) page 1 -page 11 ----	1-5, 10-12, 14,15
Y	EP 0 834 507 A (JANSSEN) 8 April 1998 (1998-04-08) cited in the application page 1 -page 5; claims; tables 2-5 ----	1-5, 10-12, 14,15
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 13499 A (JANSSEN) 9 May 1996 (1996-05-09) cited in the application page 0; claims; tables 10,11 ----	1-5, 10-12, 14,15
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